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(51) International Patent Classification ⁶ : C07D 501/00, 501/04	A1	(11) International Publication Number: WO 98/06723 (43) International Publication Date: 19 February 1998 (19.02.98)
(21) International Application Number: PCT/EP97/04439 (22) International Filing Date: 13 August 1997 (13.08.97) (30) Priority Data: A 1468/96 14 August 1996 (14.08.96) AT (71) Applicant (for all designated States except US): BIOCHEMIE GESELLSCHAFT MBH [AT/AT]; A-6250 Kundl (AT). (72) Inventors; and (75) Inventors/Applicants (for US only): MILLER, Ludwig [AT/AT]; Dreieiligenstrasse 33, A-6020 Innsbruck (AT). STURM, Hubert [AT/AT]; Leopoldstrasse 40, A-6020 Innsbruck (AT). (74) Agent: ROTH, Bernhard, M.; Novartis AG, Patent- und Markenabteilung, Lichtstrasse 35, CH-4002 Basel (CH).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: AMINE SALTS (57) Abstract Cefixime in form of a salt with dicyclohexylamine, e.g. a bis-dicyclohexylammonium salt, a process for its preparation and its use in the purification of cefixime.		

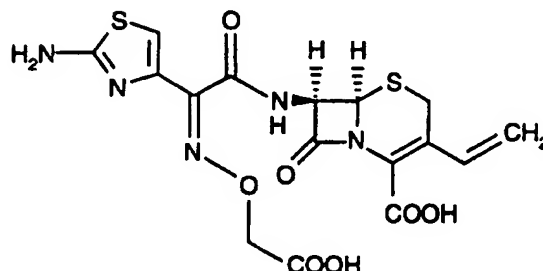
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Amine Salts

The present invention relates to cephalosporins, in particular to cefixime of formula



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more particularly to new amine salts of cefixime useful, e.g. in the purification of cefixime.

Cefixime, e.g. in form of the trihydrate is an orally available cephalosporin having e.g. excellent
 10 antibacterial properties; see e.g. H. Yamanaka et al., J. Antibiotics (1985), 38 (12), p. 1738-1751.
 The last step in the production of cefixime is described therein to be performed by acidic cleavage
 of protecting groups from protected cefixime, e.g. from cefixime wherein one or both -COOH
 groups are protected, e.g. from the compound 2-(2-amino-4-thiazolyl)-2-(tert.butoxycarbonyl-
 methoximino)acetamido)-3-vinyl-3-cephem-4-carboxylic acid-benzhydrylester with trifluoroacetic
 15 acid/anisole in yields of only 34.1%. Purification via a subsequent chromatography step is
 described.

Cleavage of such protecting groups as described above is described to be effected in mixtures of
 conc. HCl/formic acid or acetic acid; p-toluenesulphonic acid/formic acid or acetic acid; and
 methane sulphonic acid/acetic acid or formic acid; e.g. in EP 0 030 630, example 266. Cefixime
 20 being precipitated in form of an acid addition salt by addition of diisopropylether is, however,
 obtained in crude and impure form.

Cleavage of such protecting groups using aluminium trichloride and anisole is described in
 WO 95/33753. The hydrochloride of cefixime is formed and isolated from which crude cefixime is
 set free and purified via chromatography. Beside the disadvantage of the corrosive characteristics
 25 of hydrochloric acid which is to be used aluminium is present in the reaction mixture which is
 difficult to be separated off.

According to the present invention surprisingly cefixime of formula I was found in form of a salt
 with dicyclohexylamine which is particularly useful in the purification of cefixime, and which may
 30 be isolated in excellent purity, e.g. in crystalline form, containing less than 5%, even less than 3%

of by-products. The isolated salt may be converted into cefixime of high purity, e.g. in form of a solvate, e.g. hydrate, e.g. trihydrate without any further purification.

Thus, in one aspect the present invention provides cefixime of formula I in form of a salt with dicyclohexylamine.

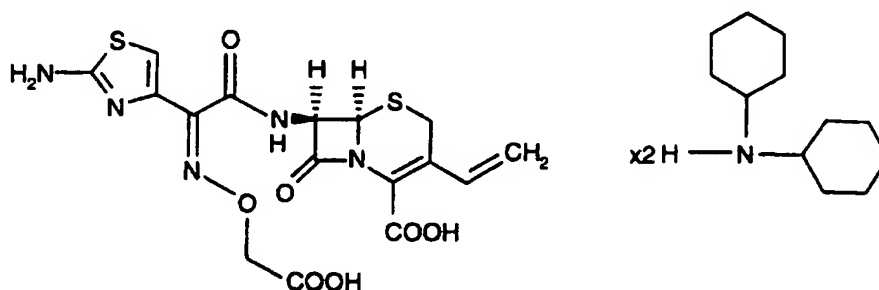
A salt of a compound of formula I with dicyclohexylamine includes a solvate, e.g. a hydrate, e.g. a trihydrate thereof.

Furthermore it was found that cefixime in form of a salt with dicyclohexylamine may crystallize.

In another aspect the present invention provides cefixime of formula I in form of a crystalline salt with dicyclohexylamine.

Furthermore it was found that cefixime in form of a bis-dicyclohexylammonium salt may crystallize. A bis-dicyclohexylammonium salt of cefixime is believed to be composed of about 1.6 to 2.4, e.g. 1.8 to 2.2, such as 1.9 to 2.1 such as 2 mol of dicyclohexylamine per mol of cefixime of formula I.

In another aspect the present invention provides cefixime of formula I in form of a bis-dicyclohexylammonium salt, e.g. of formula



A compound of formula I in form a salt with dicyclohexylamine may be produced as follows:

25 Cefixime of formula I, e.g. in free form, in form of a solvate, e.g. hydrate, e.g. trihydrate; in form of a salt, e.g. an acid addition salt, such as an acid addition salt as obtainable in a process for the production of a compound of formula I by cleavage of protection groups, e.g. a salt of a compound of formula I with hydrochloric acid, formic acid, acetic acid, a toluenesulphonic acid a methansulphonic acid; or a mixed salt of a compound of formula I, e.g.

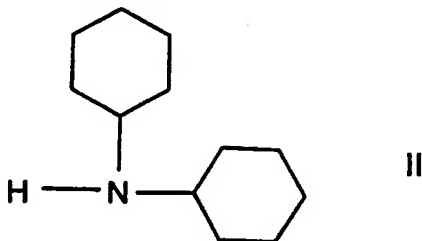
30 with two or more acids, as described above; and in form of a salt and solvate, e.g. hydrate, e.g.

trihydrate may be suspended or dissolved in a solvent or solvent system, e.g. in an organic solvent, e.g. in the presence of water.

An appropriate organic solvent includes any solvent wherein a compound of formula I may exist in form of a salt with dicyclohexylamine, e.g. in form of a solvate,, such as ketones, e.g. an alkyl ketone, preferably a dialkyl ketone such as acetone, diethyl ketone and methylisobutyl ketone; an alcohol, preferably an alkyl alcohol, e.g. methanol, ethanol or one of the isomeric propanols; a nitrile, preferably an alkyl nitrile having altogether 2 to 5 carbon atoms, for example acetonitrile; an carboxylic acid ester, for example an alkyl ester of an alkyl carboxylic acid, the carboxylic acid having altogether 1 to 8, e.g. 1 to 6 carbon atoms, e.g. acetic acid, propionic acid, such as acetic acid-(C₁ to C₄)alkylester; and an amide of a carboxylic acid, e.g. an N-dialkylamide, such as dimethylformamide. A solvent system comprising mixtures of individual solvents, e.g. as described above may be used. If not otherwise defined herein alkyl includes (C₁₋₁₂)alkyl, e.g. (C₁₋₆)alkyl, such as (C₁₋₆)alkyl, e.g. (C₁₋₄)alkyl.

Water may be present in the organic solvent or solvent system which may support solubility of cefixime in a form as described above, e.g. in form of an acid addition salt. Preferably acetone, e.g. in the presence of water may be used as organic solvent (system). In case that acetone/water is used the ratio is in principle not critical, but preferably a small amount of water in respect with acetone may be used. For suspending or dissolving a compound of formula I in a form as described above, e.g. in form of a salt, an appropriate acetone:water ratio includes 1:1 or less up to 20:1 or more, such as 2:1 to 10:1, e.g. 3:1 to 6:1.

The suspension or solution comprising a compound of formula I in a form as described above and an organic solvent with or without water may be combined with dicyclohexyl amine of formula



e.g. by addition of dicyclohexyl amine to the solution or suspension, e.g. as such, or in solution or suspension of a solvent, e.g. in a solvent as described above. An amount of dicyclohexyl amine sufficient to result in a salt of a compound of formula I with dicyclohexyl amine may be used, e.g. per equivalent of cefixime one equivalent of dicyclohexyl amine and more, e.g. 2.0 to 5.0, such as 2.2 to 4.0 equivalents may be added. In case of using a compound of formula I, e.g. in free or solvate form, per equivalent cefixime preferably 2.2 to 3.0 equivalents, in case of using a

compound of formula I in salt, e.g. in salt and solvate form, preferably 3.2 to 4.0 equivalents of dicyclohexylamine may be used.

A compound of formula I in form of a salt with dicyclohexylamine may crystallize and may be isolated as usual, for example by filtration. An anti-solvent, for example an ether or a hydrocarbon or a ketone, e.g. acetone in big excess, may be added to the reaction mixture, e.g. in case that a compound of formula I in form of a salt with dicyclohexylamine is too readily soluble in the solvent or solvent system.

If desired, an isolated compound of formula I in form of a salt with dicyclohexylamine may be resuspended in a solvent or solvent system wherein a salt of a compound of formula I is preferably insoluble or only slightly soluble and wherein impurities are soluble, such as organic solvents as described above to effect further purification.

In another aspect the present invention provides a process for the production of a compound of formula I in form of a salt with dicyclohexylamine, comprising the steps

- (i) suspending or dissolving a compound of formula I, e.g. in free form, in form of a solvate, in form of a salt, or in form of a salt and a solvate in a solvent,
- (ii) treating the suspension or solution obtained in step (i) with dicyclohexylamine, and
- (iii) isolating a compound of formula I in form of a salt with dicyclohexylamine obtained in step (ii).

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An impure cefixime, e.g. a composition containing cefixime and by-products, e.g. in free form, in form of a solvate, in form of a salt and in form of a salt and a solvate, e.g. as obtainable by acidic cleavage of protecting groups from protected cefixime, e.g. from cefixime wherein one or both -COOH groups are protected may contain considerable amounts of by-products, e.g. 6%, 7% and more. Surprisingly, cefixime in form of a salt with dicyclohexylamine may be obtained according to a process of the present invention, e.g. from impure cefixime, in highly pure, e.g. crystalline form, containing a lower amount of by-products, e.g. below 5%, even below 3%, e.g. a composition containing cefixime and by-products, e.g. less than the starting composition, may be obtained. Formation of cefixime in form of a salt with dicyclohexylamine according to the present invention may thus decrease considerably the content of by-products of an impure cefixime used as starting compound and may thus be used in the purification of impure cefixime.

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In another aspect the present invention provides the use of cefixime in form of a salt with dicyclohexylamine in the purification of impure cefixime.

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Cefixime, e.g. in free form or in solvate, e.g. hydrate, e.g. trihydrate form may be obtained from a compound of formula I in form of a salt with dicyclohexylamine, e.g. in salt and solvate form, for example as follows:

- 5 Cefixime in form of a salt with dicyclohexylamine may be dissolved or suspended in water or a mixture of water and an organic solvent. An appropriate organic solvent includes any organic solvent wherein cefixime in free form or in solvate form may exist, preferably an organic solvent as described above for the formation of a compound of formula I with a salt with dicyclohexylamine, more preferably a ketone, e.g. a dialkylketone, such as acetone and an
10 alcohol, e.g. an alkyl alcohol, such as ethanol; and water, with or without the presence of an organic solvent as described above.

A solution of cefixime in the form of a salt with dicyclohexylamine in the solvent system used may be formed, which may be filtered, e.g. in the presence of carbon, e.g. activated carbon and/or a filter assistant agent and/or through an adsorber resin.

- 15 Cefixime in free form or in solvate form may precipitate by combination of a solution or suspension of cefixime in form of a salt with dicyclohexylamine with an acidic agent, e.g. by addition of an acid, to an pH where cefixime may exist in free form or in solvate form. An appropriate pH includes a pH of (about) 1.5 to 4, e.g. 2 to 3. An acidic agent includes an appropriate acidic agent which is able to convert cefixime in form of a salt with dicyclohexylamine
20 into cefixime in free form or solvate form, preferably an inorganic acid, such as phosphoric acid or sulphuric acid; an acidic ion exchange resin may e.g. be used. Cefixime in free or solvate form may crystallize and may be isolated, e.g. as usual, e.g. by filtration.

- Dicyclohexylamine may be removed, e.g. partially, e.g. prior to isolation of cefixime, e.g. by
25 extraction from the reaction mixture, e.g. prior to crystallisation of cefixime. For extraction of dicyclohexylamine the pH of the reaction mixture may be adjusted to 8 to 11, e.g. ≥ 9 , such as 9 to 11, e.g. 10 to 11, e.g. by use of a base, preferably an inorganic base, such as e.g. an alkali, e.g. sodium and potassium or earth alkali hydroxide and carbonate, preferably a hydroxide.

- Dicyclohexylamine may be extracted into an organic solvent which is able to form a two-phase
30 system with water and which is able to dissolve dicyclohexylamine, e.g. partially, in a two-phase system with water, including e.g. a halogenated hydrocarbon, such as methylene chloride, a ketone, such as methyl isobutylketone and an ester of a carboxylic acid, such as ethyl acetate, isopropyl acetate, n-butyl acetate, for example as usual. Water may be added to the reaction mixture, if not present in an amount sufficient to form a two phase system in the reaction mixture.

- 35 Dicyclohexylamine may also be removed from the reaction mixture by use of an ion exchange resin, adsorber resin and an ion retardation resin, such as AG 11 A8[®] from Biorad; Dianion

Snake cage resin[®] from Mitsubishi, styrene-divinylbenzene copolymerisates, e.g. Dianion HP 20[®], Dianion HP 21[®], Dianion SP 207[®], Amberlite XAD 1180[®], XAD 1600[®], XAD 16[®] or adsorber resins CG 161[®], e.g. by stirring the reaction mixture in the presence of such a resin or by pouring the reaction through a bed of such a resin.

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After removal, e.g. extraction of dicyclohexylamine the pH of the reaction mixture may be adjusted again to 1.5 to 4, e.g. 2 to 3 as described above, e.g. in the presence of an organic solvent, preferably in the presence of a ketone, such as an alkylketone, e.g. a dialkylketone, e.g. acetone; or an alcohol, such as an alkyl alcohol, e.g. ethanol. Cefixime, e.g. in free or solvate, e.g. hydrate, e.g. trihydrate form may be obtained, e.g. in crystalline form, and may be isolated, e.g. as usual.

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In another aspect the present invention provides a process for the conversion of cefixime in form of a salt with dicyclohexylamine into cefixime comprising the steps

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- (i) combining an acidic agent with cefixime in form of a salt with dicyclohexylamine in a solvent, and
- (ii) isolating cefixime obtained in step (i).

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Cefixime in form of a salt with dicyclohexylamine may be obtained in substantially pure form, but depending on the content of the impurities of impure cefixime used as starting compound for its production, it may still contain considerable amounts of impurities, e.g. impure cefixime in form of a salt with dicyclohexylamine, e.g. a composition containing cefixime and, e.g. more than 2% by-products may be obtained. It was now surprisingly found that the conversion of cefixime in form of a salt with dicyclohexylamine into cefixime may considerably decrease the amount of impurities, e.g. the content of by-products present in a composition containing cefixime and by-products used as a starting material in a process according to the present invention. Cefixime may be obtained from the conversion step in highly pure form, e.g. crystalline form and may contain low amounts of by-products, e.g. below 1.2%, even below 0.7%.

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In another aspect the present invention provides a process for the depletion of by-products in a composition containing cefixime and by-products, comprising converting cefixime into a salt with dicyclohexylamine and isolating cefixime in form of salt with dicyclohexylamine, and/or converting cefixime in form of a salt with dicyclohexylamine into cefixime and isolating cefixime.

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In another aspect the present invention provides the use of a process for converting cefixime in form of a salt with dicyclohexylamine, e.g. a crystalline salt, e.g. a bis-dicyclohexylammonium salt, into cefixime in the purification of cefixime.

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In another aspect the present invention provides a process for the purification of impure cefixime comprising the steps

- (i) producing a salt of cefixime with dicyclohexylamine,
- (ii) producing cefixime from a salt obtained in step (i), and
- 10 (iii) isolating cefixime obtained in step (ii).

Such a process has the advantage that impurities of an impure cefixime, e.g. a composition containing cefixime and by-products used as starting material, e.g. in the range of about 6% and more may be decreased to a content of e.g. 0.7% and below.

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A salt of a compound of formula I with dicyclohexylamine according to the present invention may be produced easily, even without the use of halogenated solvents, if desired and may decrease considerably the content of by-products, if used in any purification process according to the present invention. A process according to the present invention may be used on technical scale.

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A salt of the present invention may thus be used in the purification of impure cefixime. Purified cefixime in form of a trihydrate obtained according to the present invention may be used, if desired after further purification, as an antibacterial agent in the same dosages and in the same applications as purified cefixime in form of a trihydrate obtainable according to known
25 (purification) processes.

The following non-limitative examples illustrate the present invention.

All temperatures are given in °Celsius.

Cefixime is also known under the chemical names

- 30 [6R-(6 α ,7 β (Z))-7-[[2-amino-4-thiazolyl][(carboxymethoxy)imino]acetyl]amino]-3-ethenyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid; or
- (7-[2-(aminothiazol-4-yl)-2-(carboxymethoximino)acetamido-3-vinyl-3-cephem-4-carboxylic acid.

The content of by-products was determined by HPLC and is given in % of the peak area.

The chemical nature of the by-products was not determined.

Example A**Production of impure cefixime by acidic cleavage of a -COOH protecting group in protected cefixime****a) Impure cefixime in form of a salt with p-toluene sulphonic acid**

- 5 A solution of 150 g 7-[2-(2-aminothiazol-4-yl)-2-(tert.-butoxycarbonylmethoximino)acet-amido]-3-vinyl-3-cephem-4-carboxylic acid in 480 ml of formic acid is treated with 67,2 g of a hydrate of p-toluene sulphonic acid at 0°. The reaction mixture is stirred for ca. 6 hours and poured into 6,2 l of methyl-tert.-butylether within ca. 15 minutes. Stirring is continued for ca. 1 hour at room temperature. Cefixime in form of a salt with p-toluenesulphonic acid precipitates, is filtrated off, washed with methyl-tert.-butylether and dried.
- 10 Yield: 117,5 g in form of a white, amorphous powder
Content of by-products (HPLC) : 7,16 %.

b) Impure cefixime in form of a trihydrate

- 15 5 N KOH are added dropwise to a suspension of 64,6 g impure cefixime in form of a salt with p-toluene sulphonic acid (content of by-products: 7,16 %), obtainable according to example Aa), in 650 ml of water at 20° adjusting a pH of 5,8. The solution is filtrated, the pH of the filtrate is adjusted to 2.5 by addition of 5 M sulphuric acid within ca. 45 minutes and the reaction mixture is stirred for ca. one hour at room temperature and ca. 2 hours at 0°. Cefixime in form of a trihydrate precipitates, is washed with water and dried.
- 20 Yield: 40,9 g in form of a white, crystalline powder.
Content of by-products: 5.76 %

Example 1**Production of cefixime in form of a bis-dicyclohexylammonium salt**

- 25 15 g of dicyclohexylamine are added dropwise to a suspension of 15 g of impure cefixime in form of a trihydrate (content of by-products: 5.76%), obtainable according to example Ab) in a mixture of 60 ml of acetone and 15 ml of water. A solution is obtained. 540 ml of acetone are added dropwise within 30 minutes at 20°. Cefixime in form of a bis-dicyclohexylammonium salt crystallises. The crystal suspension is stirred for ca. one hour at room temperature, cooled to 0° and stirred for 2 hours at 0°. Cefixime in form of a bis-dicyclohexylammonium salt is filtrated off, washed with acetone and dried.
- 30 Yield: 21.7 g in form of a white, crystalline powder.
Content of by-products: 2.59%
Melting point: 175° (decomp.).

¹H-NMR spectrum (DMSO-d₆): 0.90-2.30 (m, 40H, cyclohexyl-H); 3.03 (m, 4H, cyclohexyl-H); 3.46 (s (broad), 2H, S-CH₂); 4.33 (s, 2H, O-CH₂-); 4.96 (d, J=8.0Hz, 1H, vinyl-H); 5.12 (d, J=5.4Hz, 1H, β-lactam-H); 5.16 (d, J=18.0Hz, 1H, vinyl-H); 5.68 (m, 1H; β-lactam-H); 6.83 (s, 1H, thiazolyl-H); 6.93 (dd, J=12.0 & 18.0Hz, 1H, vinyl-H).

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Example 2

Production of cefixime in form of a trihydrate

- A solution of 5 g of cefixime in form of a bis-dicyclohexylammonium salt (content of by-products: 2.59 %), obtainable according to example 1, in 50 ml of water is mixed with 1 g of activated carbon, stirred for 10 minutes at room temperature, and filtered. The filtrate is diluted with 20 ml of ethanol and the pH is adjusted to 2.5 by dropwise addition of 2 ml of sulphuric acid within ca. 45 minutes. Cefixime in form of a trihydrate crystallises. The reaction mixture is stirred for ca. 1 hour at room temperature for ca. 1 hour at 0°. Crystalline cefixime in form of a trihydrate is filtrated off, washed with water and dried.
- Yield: 2.78 g in form of a white, crystalline powder.
- Content of by-products: 0.62 %

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Example 3

Production of cefixime in form of a trihydrate

- A solution of 5 g of cefixime in form of a bis-dicyclohexylammonium salt (content of by-products: 2.59%), obtainable according to example 1, in 50 ml of water is mixed with 25 ml of methylene chloride and cooled to 0°. 6.1 ml of 2 M NaOH are added dropwise under stirring and the phases are separated. The methylene chloride phase contains dicyclohexylamine. The aqueous phase is washed with methylene chloride, treated with 1 g of activated carbon, stirred for 10 minutes in an ice bath and filtrated. Isolation of crystalline cefixime in form of a trihydrate from the filtrate is performed after adjustment of the pH to 2.5 as described in Example 2, according to the method as described in Example 2.
- Yield: 2.78 g
- Content of by-products: 1.13%

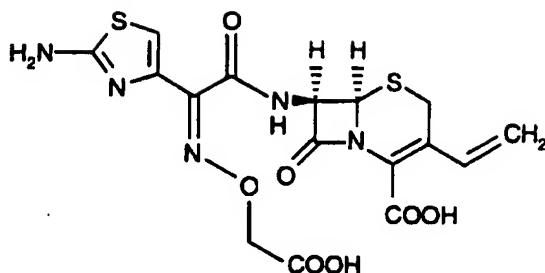
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Claims:

1. Cefixime of formula

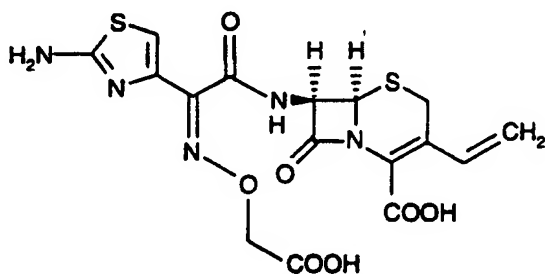
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in form of a salt with dicyclohexylamine.

2. A salt according to claim 1 which is crystalline.
3. A salt according to any one of claims 1 or 2 which is a bis-dicyclohexylammonium salt.
4. A process for the production of a compound of formula

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in form of a salt with dicyclohexylamine, comprising the steps

- (i) suspending or dissolving a compound of formula I
in a solvent,
- (ii) treating the suspension or solution obtained in step (i) with dicyclohexylamine, and
- (iii) isolating a compound of formula I in form of a salt with dicyclohexylamine obtained in
step (ii).

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5. A process according to claim 4, characterized in that in step (i) the starting compound of formula I is in free form, in form of a solvate, in form of a salt, or in form of a salt and a solvate.
- 5 6 Use of cefixime in form of a salt with dicyclohexylamine in the purification of impure cefixime.
7. A process for the conversion of cefixime in form of a salt with dicyclohexylamine into cefixime comprising the steps
- 10 (i) combining an acidic agent with cefixime in form of a salt with dicyclohexylamine in a solvent, and
- (ii) isolating cefixime obtained in step (i).
8. A process for the depletion of by-products in a composition containing cefixime and by-products, comprising
- 15 converting cefixime into a salt with dicyclohexylamine and isolating cefixime in form of salt with dicyclohexylamine, and/or
- converting cefixime in form of a salt with dicyclohexylamine into cefixime and isolating cefixime.
- 20 9. Use of a process for converting cefixime in form of a salt with dicyclohexylamine into cefixime in the purification of cefixime.
10. A process for the purification of impure cefixime comprising the steps
- 25 (i) producing a salt of cefixime with dicyclohexylamine,
- (ii) producing cefixime from a salt obtained in step (i), and
- (iii) isolating cefixime obtained in step (ii).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/04439

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D501/00 C07D501/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 33753 A (MARCHAM TRADING & INVESTMENT LTD) 14 December 1995 cited in the application see the whole document	1
A	EP 0 030 630 A (FUJISAWA PHARMACEUTICAL CO. LTD) 24 June 1981 cited in the application see page 246 - page 247; claim 2	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

13 January 1998

Date of mailing of the international search report

20/01/1998

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/04439

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